REMARKS

Claims 1-11, 15-18, 20, 21, 45-51, and 59-60 are currently pending and under consideration. By virtue of this amendment, claims 20 and 51 have been amended. Support for the claim amendments may be found throughout the application as filed as well as the underlying provisional applications. In particular, support for the amendments to claims 20 and 51 may be found, for example, in the instant application as filed at page 6, lines 8-18, and in U.S. provisional application 60/408,571 at page 4, lines 12-14. No new matter has been introduced.

Amendments of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The amendments are being made solely to expedite prosecution of the present application. Applicant reserves the option to further prosecute the same or similar claims in the instant or subsequent application.

Applicant respectfully requests reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicant acknowledges with appreciation the indication in the Office Action mailed April 18, 2011 that Applicant's Amendment filed on January 25, 2011 has overcome the objections to the claims as well as the rejections under 35 U.S.C. §112, second paragraph; 35 U.S.C. §112, first paragraph, written description; and 35 U.S.C. §112, first paragraph, enablement.

Priority

The Wang Declaration

At pages 4 and 5 of the Office Action, Applicant's asserted effective priority date of at least 20 December 2001 was refused. According to the Office Action, "the Wang 131 declaration"[1] and its supporting materials [hereinafter collectively the Declaration], upon which the asserted priority claim is based, allegedly do "not provide for the generic anti-C5 antibodies that inhibit the conversion of C5 into C5a and C5b, as currently claimed." Office Action at page 4 (underlining in original). The Examiner urges that

[1] The Declaration was submitted with Applicant's 25 January 2011 Amendment and Response to Non-final Office Action.

> there is no disclosure [in the Declaration] that the generic properties of anti-C5 antibodies…in the context of the claimed invention was [sic] described in a manner that provides for conception, diligence and reduction to practice prior to the claimed invention in a manner that obviates the prior art teachings.

Id. (underlining in original). Moreover, the Examiner casts doubt as to whether BB5.1, a specific anti-C5 antibody recited in the Declaration, is actually a member of the instantly claimed genus of anti-C5 antibodies. Applicant respectfully disagrees with this position.

At bottom, the Examiner's refusal of the priority claim sounds in written description – that the Declaration allegedly fails to provide: (a) literal support for the properties of the claimed genus of antagonist anti-C5 antibodies (i.e., anti-C5 antibodies that inhibit the conversion of complement component C5 into C5a and C5b); and/or (b) sufficient representative species to support the genus. As an initial matter, a proper legal analysis of whether written description is satisfied "calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention." M.P.E.P. § 2163 (II)(A)(2). This analysis should be "conducted from the standpoint of one of skill in the art [at the relevant time]…and should include a determination of the field of the invention and the level of skill and knowledge in the art." *Id.*

Applying this legal rubric, it is clear that the Examiner's position simply cannot stand under the weight of an objective reading of the Declaration in conjunction with the common scientific knowledge in the art on or around 20 December 2001. A skilled artisan would have readily, easily, and completely understood from the Declaration that Applicant conceived of a therapeutic use of a genus of antagonist anti-C5 antibodies that inhibit cleavage of C5 into fragments C5a and C5b at least by 20 December 2001.

Exhibit A of the Declaration, for example, leads with a broadly stated purpose: to "Evaluate the efficacy of ***anti-C5*** (BB5.1) on asthma mouse model." (Emphasis added.) Save once, the inventor consistently refers to an "anti-C5" antibody, rather than a specific antibody (e.g., BB5.1), throughout Exhibits A and B of the Declaration.

The Examiner, in this aspect of his argument, reads the term "anti-C5" narrowly; one of ordinary skill in the art on or around 20 December 2001 would not have. Rather the skilled artisan would have readily and unambiguously appreciated that "anti-C5" and/or "anti-C5 antibody" were terms of art referring to a genus of antibodies that inhibit the cleavage of C5 into fragments C5a and C5b, as is instantly claimed. To bolster Applicant's position, copies of Wang et al. (September 1995) *Proc Natl Acad Sci USA* 92:8955-8959[2] [hereinafter Wang et al.] and PCT application publication no. WO 95/29697[3] [hereinafter the '697 PCT] are submitted herewith[4]. As elaborated on below, each reference demonstrates that: (i) the term "anti-C5" antibody is and was on or around 20 December 2001 used to describe a genus of antibodies that inhibit C5 cleavage into fragments C5a and C5b; and (ii) specific anti-C5 antibodies, such as BB5.1, were tested in animal models primarily to establish proof of concept for therapeutic C5 inhibition in human disease.

For example, Wang et al. describes the results of experiments evaluating the role of terminal complement in arthritis. As in the instant case, the authors of Wang et al. test a specific murine anti-C5 antibody (BB5.1) in a mouse model of disease. To remove any doubt, BB5.1 is, and was well-known in the art for many years to be, "an inhibitory mAb specific for murine C5" that "effectively inhibits terminal complement activation *in vivo*." *Id.*, at 8955, column 2. *See also* the '697 PCT, at Example 4, page 46.

Analogous to the Declaration, the therapeutic objective of the Wang et al. authors was not to treat arthritis in *mice*. Rather, the aim was generally "[t]o target complement activation in immune-mediated joint inflammation [using] monoclonal antibodies that inhibit the complement cascade at C5, blocking the generation of…C5a and C5b-9." Wang et al., at page 8955, Abstract. Wang et al.'s results provided "persuasive evidence that C5-specific mAb therapy may be an effective approach to the treatment of inflammatory joint disease" and supported "the derivation of a potent anti-human C5-blocking mAb[.]" Wang et al., at page 8959, column 2. In other words, *a specific*

[2] Wang et al. *Proc Natl Acad Sci USA* 92:8955-8959 (1995) was previously submitted on the Form PTO/SB/08b filed in connection with the instant application on September 22, 2006.
[3] Submitted herewith as Exhibit A.
[4] Each reference published more than six years before the priority date presently asserted by Applicants. Yi Wang, the author of the Declaration, is the first author of Wang et al. and an inventor named in the '697 PCT.

anti-C5 antibody served as a surrogate to establish proof of concept for use of functionally-related anti-C5 antibodies in human disease.

Similarly, the '697 PCT relates to, among other things, methods for treating a human afflicted with glomerulonephritis (GN). The '697 PCT at page 1. The inventors of the '697 PCT evaluated the antagonist anti-C5 antibody BB5.1 in a GN mouse model. *Id.*, at pages 43 to 46 (anti-C5 monoclonal antibodies used in the experiment are described at page 41, line 34 to page 42, line 1). As with Wang et al., treating mice was not the core objective. Based, at least in part, on the experimental evidence in the '697 PCT's specification, the PCT's inventors concluded that "antibodies [that] block the generation…of complement components C5a and C5b" are useful for treating glomerulonephritis in humans. *Id.*, at page 11, lines 7 to 31.

Thus, it is clear that a skilled artisan on or around 20 December 2001 reading the notebook pages of the Declaration would have at once understood that "[evaluating] the efficacy of ***anti-C5*** (BB5.1) on asthma mouse model", as asserted by the inventors, referred to the surrogate evaluation of BB5.1 as indicative of the therapeutic effect of a genus of functionally-related anti-C5 antibodies, rather than to use of BB5.1 *per se*. Accordingly, the artisan would have appreciated that the instant inventor had conceived of the therapeutic use of antagonist anti-C5 antibodies at least by 20 December 2001. Moreover, as evidenced by the working examples of the priority application (U.S. patent application serial no. 60/408,571), the inventor diligently carried out and completed the experiments described in the Declaration.

Notwithstanding these considerations, and in an alternative argument, the Office finds enormous breadth in the term "anti-C5" in order to conclude that Applicant impermissibly claims an unsupported subgenus (namely antagonist anti-C5 antibodies that inhibit the conversion of complement component C5 into C5a and C5b) within the broader genus of anti-C5 antibodies. Office Action at page 4. Under the Examiner's definition, ostensibly, "anti-C5 antibodies" as used in the Declaration include those antibodies that inhibit C5 cleavage (antagonist antibodies) and those that do not. In this embodiment of the argument, the Examiner alleges that BB5.1, an anti-C5 antibody that inhibits C5 cleavage, is simply not enough to support this "subgenus" of antagonist

anti-C5 antibodies. Applicant disagrees with the Examiner's characterization for at least the following reasons.

First, it is simply axiomatic that Applicant is free to be his own lexicographer when his description makes clear the definition of the claim term at issue. M.P.E.P § 2173.05(a)(III). As discussed *supra*, a skilled artisan on or around 20 December 2001 would have readily and unambiguously understood that the term "anti-C5" antibody – as used by the inventor in the Declaration, the instant application, and the art for years prior to the instantly asserted priority date – is and was coextensive with a genus of antagonist anti-C5 antibodies that inhibit the cleavage of C5 into fragments C5a and C5b. In fact, it defies reason that a skilled artisan in the complement field would have believed that the inventor, who has investigated the therapeutic role of C5 inhibition for decades, conceived of the *therapeutic* use of antibodies that do not inhibit C5 cleavage.

Furthermore, in contrast to the Office's position, a skilled artisan on or around 20 December 2001 would have been well aware of numerous, well-known species of antagonist anti-C5 antibodies embraced by the instant claims. The Office Action, for example, acknowledges that at least one example, BB5.1, is expressly provided in the Declaration. And, even if not explicitly recited in the Declaration, the skilled artisan would also have been well aware that additional "anti-C5 antibodies that have the desirable ability to block complement hemolytic activity and to block the generation of C5a…***have been known in the art since at least 1982***." The '697 PCT, at page 28 (emphasis added).

The Court of Appeals for the Federal Circuit (CAFC) has stated that "[i]nformation", such as information relating to additional antagonist anti-C5 antibodies embraced by the claims, "which is well known in the art need not be described in detail in the specification." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 1380 (Fed. Cir. 1986). In this case, such well-known information includes, e.g., the antagonist anti-C5 antibodies 5G1.1 and 5G1.1 scFv as described in, e.g., the '697 PCT at page 28. The well-known information also includes the N19/8 and N19/8 scFv antibodies (see, e.g., the '697 PCT) as well as the antagonist anti-C5 antibodies described in Moongkarndi et al. (1982) *Immunobiol* 162:397 and Moongkarndi et al. (1983)

Immunobiol 165:323, copies of each of which are also submitted herewith as Exhibits B and C, respectively. In fact, the Office Action acknowledges that "eculizumab or pexelizumab, which are the same anti-C5 antibodies recited in instant claim 49 and encompassed by anti-C5 antibodies that inhibit the conversion of C5 into fragments C5a and C5b", were also known in the art on or around 20 December 2001.

Thus, whether express or implicit by virtue of common scientific knowledge, the Declaration materials adequately describe a sufficient number of species representative of the claimed genus to legally establish possession. *See*, e.g., M.P.E.P. § 2163 II(A)(3)(a)(ii). It is clear that a skilled artisan on or around 20 December 2001 would have readily and easily understood from the Declaration that Applicant has possession of a genus of antagonist anti-C5 antibodies, as is instantly claimed. Accordingly, acknowledgement of Applicant's asserted priority date of at least 20 December 2001 is requested.

U.S. Provisional Patent Application No. 60/408,571

At page 4 of the Office Action, a 6 September 2002 priority date, based on U.S. provisional patent application no. 60/408,571, was recognized for claims 1 to 11, 12 to 18, 45 to 50, 59, and 60, but was denied to claims 20 and 51. According to the Examiner, allegedly there is insufficient written description support for the combination therapies embraced by claims 20 and 51. Applicant respectfully disagrees.

Instant claims 20 and 51, as amended, are drawn to combination therapies in which an anti-C5 antibody is administered in combination with at least one asthma therapy regimen selected from the group consisting of steroids, anti-IgE antibodies, anti-IL-4 antibodies, anti-IL-5 antibodies, β2 adreno receptor agonists, leukotriene inhibitors, 5 Lipoxygenase inhibitors, PDE inhibitors, CD23 antagonists, IL-13 antagonists, cytokine release inhibitors, histamine H1 receptor antagonists, anti-histamines and histamine release inhibitors.

Ipsis verbis support for such combination therapies can be found in the present application (page 6, lines 8 to 18) as well as in U.S. serial no. 60/408,571 at page 4, lines 12 to 14, which reads:

"[a] combination therapy may also be used that includes a complement-inhibiting compound in combination with a regimen of known asthma therapy, such as, for example, steroid, anti-IgE antibody, anti-IL-4 or anti-IL-5 antibody." In addition to providing literal support for the instantly claimed genus of known asthma therapy regimens, the cited text, in fact, serves two other purposes. First, it expressly provides four specific species – steroids, anti-IgE antibodies, anti-IL-4 antibodies, and anti-IL-5 antibodies – of the genus of known asthma therapy regimens, each of which is recited in the instant claims. (The priority document also exemplifies the use of a combination of an anti-C5 antibody and the steroid dexamethasone[5].) Second, through use of the word "known", the description emphasizes that additional species of *known* asthma therapy regimens were in the art at the effective filing date of the application.

As noted above, "[i]nformation which is well known in the art need not be described in detail in the specification." *Hybritech, Inc.*, 802 F.2d at 1379, 1380. *See also* M.P.E.P. § 2165 (II)(A)(2). In this case, the skilled artisan at the effective filing date of the application, upon reading the priority application, would have at once recognized that, e.g., the β2 receptor agonists, PDE inhibitors, anti-histamines, and cytokine release inhibitors recited in the instant claims were all well-known asthma therapy regimens in the art of medicine. The Office Action at least implicitly acknowledges this fact by citing Krause (*infra*).

In conclusion, the priority document provides literal support for the genus of known asthma therapy regimens instantly claimed. It also provides literal support for at least four species embraced by that genus. Additional species of known asthma therapy regimens were well-known in the art. Thus, upon reading the priority document, a person of ordinary skill in the art would have easily and readily understood that Applicant was in possession of the claimed genus. Accordingly, acknowledgment of Applicant's priority claim of at least 6 September 2002 for claims 20 and 51 is respectfully requested.

[5] *See* U.S. provisional patent application serial no. 60/408,571 at pages 15 to 19.

Claims Rejected Under 35 U.S.C. §102(e)

At pages 5 to 8 of the Office Action, claims 1 to 11, 15 to 18, 20, 21, 45 to 51, 59, and 60, were rejected under 35 U.S.C. § 102 as allegedly being anticipated by Krause (U.S. patent application publication no. 2004/0014782) [hereinafter Krause]. Applicant traverses.

First, Applicant maintains that Krause is not properly § 102(e) prior art against the instant application for the reasons of record and those provided herein. In short, the Declaration clearly establishes that Applicant conceived of the instant invention prior to March 29, 2002, the filing date of the priority application of Krause, and was diligent from prior to March 29, 2002 to at least September 6, 2002. Accordingly, Krause cannot serve as a § 102(e) reference against the instant application, and reconsideration and withdrawal of this rejection are respectfully requested.

Assuming *arguendo* that Krause could serve as prior art against the instant application, though it should not, Applicant maintains that Krause does not disclose a method for treating asthma or other pulmonary diseases using an anti-C5 antibody as is instantly claimed.

In order to anticipate the instant claims, Krause must disclose, either expressly or inherently, each and every element of the claimed methods. *See*, e.g., *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628 (Fed. Cir. 1987) as cited in M.P.E.P. § 2131. Krause does not satisfy these requirements.

Krause discloses candidate small molecule C5a antagonists and their use, alone or in combination with other "C5a receptor-inactive agents", to treat inflammatory and/or autoimmune disorders such as rheumatoid arthritis (RA), skin injuries, infections, and lung diseases such as asthma. At paragraphs [0027] and [0277], eculizumab and pexelizumab are recited as one of many different examples of other "C5a receptor-inactive agents" that can be used in combination with the small molecules for treating RA. Anti-C5 antibodies have no effect on preformed C5a; the antibodies are not embraced by Krause's definition of C5a antagonist. At page 6, the Examiner appears to concede these points.

However, the Office Action advances yet another theory of anticipation: even though eculizumab and pexelizumab are not "C5a antagonists" *per se*, as defined by Krause, nor are they

expressly mentioned in Krause's asthma-related disclosure, the antibodies are nonetheless "therapeutic agents" and allegedly inherently included in the asthma-related disclosure. Applicant disagrees with this argument as well.

The legal standard for inherent anticipation is well established – "the extrinsic evidence 'must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citations omitted) (emphasis added). "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." M.P.E.P. § 2112 citing *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) (emphasis in original). The initial burden of proof falls upon the Office. *See*, e.g., M.P.E.P. § 2112 (IV) (stating "'In relying upon a theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art.'") (Emphasis in original.) Applicant asserts that the Office has not established a *prima facie* case of inherent anticipation for at least the following reasons.

First, as discussed in Applicant's 25 January 2011 Amendment and Response to Non-final Office Action, Krause discloses in a distinct and modular way specific combination therapies useful for treating different types of inflammation. That is, in each therapeutic "module" related to the treatment of a specific inflammatory condition (e.g., rheumatoid arthritis), Krause discloses specific C5a receptor-inactive agents that can be used in combination with the C5a receptor antagonists of its disclosure. For example, at pages 17 and 18, Krause discloses a combination therapy for treating rheumatoid arthritis, which therapy includes "at least one C5a antagonist and a C5a receptor-inactive agent that is an anti-arthritic agent (i.e., a C5a receptor-inactive anti-arthritic agent)." *Id.* at paragraph [0202]. In another therapeutic module, Krause provides a combination therapy for treating lung disorders using at least one C5a antagonist and a C5a receptor-inactive agent "useful in the treatment of asthma." *Id.* at paragraph [0227] and paragraph [0279].

Eculizumab and pexelizumab are recited only two times in Krause, and in each instance only in "rheumatoid arthritis" therapeutic modules and only as one of a laundry list of well-known,

potential C5a receptor-inactive anti-arthritic agents. In contrast, the two therapeutic modules drawn to treating lung disorders – at pages 18, 19, and 23 of Krause – do not mention eculizumab or pexelizumab, or any other anti-C5 antibodies, as being one of the C5a receptor-inactive agents useful for treating asthma. Instead, the lung disorder-related therapeutic modules recite a lung disorder-specific laundry list of well-known asthma treatments. Krause at paragraphs [0227] to [0229].

Since Krause does not expressly describe the use of anti-C5 antibodies, alone or in combination, to treat lung disorders such as asthma, the only way it can anticipate the claims, if at all, is by inherency. Yet neither eculizumab nor pexelizumab are ***necessarily*** part of the expansive genus of "C5a receptor inactive agents" embraced by Krause's asthma-related disclosure, as is required under the law for inherency. In fact, in view of the myriad, diverse C5a receptor-inactive agents specifically recited in paragraphs [0027] to [0029], one of ordinary skill in the art at the effective filing date of Krause would certainly not have at once placed eculizumab and/or pexelizumab, let alone even anti-C5 antibodies in general, in Krause's laundry list of C5a receptor-inactive agents useful for treating asthma.

The term "C5a receptor-inactive agent", for example, imparts no structural or functional constraints on the types of compounds embraced by the genus – other than what its members are not. Rather, the specific examples of C5a receptor-inactive agents recited in Krause's asthma-related sections are functionally and structurally diverse. For example, the genus of functionally-diverse asthma-related C5a receptor-inactive agents includes, without limitation, leukotriene modifiers, mast cell stabilizers, phosphodiesterase 4 (PDE4) inhibitors, beta adrenergic receptor agonists, and thrombin inhibitors. *Id.* The C5a receptor-inactive agents embraced by Krause's asthma-related disclosure also have no apparent unifying structural features (e.g., steroidal compounds as compared to methylxanthines or cromolyns). *Id.* Given the broad range of function and physical attributes of the specific C5a receptor-inactive agents recited at paragraphs [0027 to [0029], it can hardly be said that eculizumab and pexelizumab, or any other anti-C5 antibody, are ***necessarily*** members of the genus of C5a receptor-inactive agents useful for treating asthma, which is required under the law.

On the other hand, eculizumab and pexelizumab are actually dissimilar from Krause's C5a receptor-inactive agents for at least one important reason – neither antibody was well known, clinically approved, or the subject of clinical trials for treating asthma or any related lung condition at the effective filing date of Krause. This is, of course, in stark contrast to the specific C5a receptor-inactive agents recited at paragraphs [0227] to [0229], all of which were well-known, clinically approved, and/or the subject of clinical trials for treating asthma. For example, Aerolate®, as recited in paragraph [0227] of Krause, was FDA approved on 3 December 1986; Accolate™, as recited in paragraph [0227] of Krause, was FDA approved on 26 September 1996; Nasalcrom™, as recited in paragraph [0227] of Krause, was FDA approved on 3 January 1997; Zyflo™, as recited in paragraph [0227] of Krause, was FDA approved on 9 December 1996; Atrovent™, as recited in paragraph [0227] of Krause, was FDA approved on 29 December 1986; Vanceril™, as recited in paragraph [0228] of Krause, was FDA approved on 12 May 1976; Advair™, as recited in paragraph [0228] of Krause, was FDA approved on 24 August 2000; and Flovent™, as recited in paragraph [0228], was FDA approved on 27 March 1996. *See*, e.g., U.S. Food and Drug Administration Website (Drugs@FDA, original approval or tentative approval date). Eculizumab was, at the effective filing date of Krause, the subject of a clinical trial for the treatment of RA (hence it is included in the RA-related sections of Krause). But the skilled artisan reading Krause would not have at once grouped these anti-C5 antibodies with well-known, asthma-related secondary agents such as those disclosed by Krause. At a minimum, such antibodies would not ***necessarily*** be members of Krause's genus of C5a receptor-inactive agents useful for treating asthma, which is required under the law.

In view of the foregoing, Applicant respectfully submits that Krause fails to expressly or inherently anticipate the instant claims. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims Rejected Under 35 U.S.C. §103(a)

At pages 8 to 12 of the Office Action, claims 1 to 11, 15 to 18, 20 to 21, 45 to 51, and 59 to 60 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Krause (*supra*) in view of Evans et al. (U.S. Patent No. 6,355,245) [hereinafter Evans], Fung et al. (U.S. Patent No.

6,956,107) [hereinafter Fung (a)], Fung et al. (U.S. Patent No. 6,998,468) [hereinafter Fung (b)], Lobb et al. (U.S. Patent No. 5,871,734) [hereinafter Lobb], and the known regimens of asthma therapy. Applicant respectfully traverses.

The Examiner, relying on the obviousness standard articulated by the U.S. Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), concluded that

> [g]iven that the goal was to inhibit complement activation in order to treat pulmonary diseases…incorporating…anti-C5 antibodies into therapeutic regiments [sic] to treat…pulmonary conditions such as asthma would have been routine to the ordinary skilled artisan at the time the invention was made and therefore obvious[.]

Id., at page 12. Applicant respectfully disagrees with the Examiner's position.

While the *KSR* court did foreclose the use of argumentation based solely upon a lack of teaching, suggestion, or motivation – the *TSM test* – the Court emphasized that there must still be an *apparent reason* for the skilled artisan to combine references to arrive at the claimed invention. *KSR International Co.*, 550 U.S. at page 417 and 418. *See also* M.P.E.P. § 2143.01 (IV) (the P.T.O. stating that just "because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references.") Furthermore, the Examination Guidelines Update (2010) promulgated by the U.S.P.T.O. state that "familiar lines of argument still apply including teaching away from the claimed invention from the prior art…and unexpected results. Indeed, they have taken on ***added importance*** in view of the recognition in *KSR* of a variety of possible rationales." Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex, *Federal Register* 75(169):53643, 53645, column 3 (emphasis added).

Applicant maintains that Krause is not properly § 102(e) prior art against the instant application. Assuming *arguendo* that Krause could serve as prior art against the instant application, Applicant asserts that, absent the teachings of the instant specification, there would have been no apparent reason for a skilled artisan to modify the teachings of this reference, in view of the secondary references, and arrive at the claimed methods.

The instant claims are drawn to methods for treating respiratory disorders characterized by established airway inflammation and airway hyperreactivity commonly manifest in patients suffering from chronic asthma, an ongoing asthma attack, and/or chronic obstructive pulmonary disease (COPD). The methods include use of an anti-C5 antibody that inhibits the cleavage of C5 into fragments C5a and C5b.

The claimed methods are based, in part, on actual experimental data provided in the application exemplifying use of a terminal complement component C5 inhibitor (an anti-C5 antibody) to treat established respiratory disease. *See* instant Specification at, e.g., page 21, line 10 to page 28, line 18. For example, the inventor demonstrated, using a mouse asthma model, that administration of an anti-C5 antibody to mice with severe established inflammation, during an ongoing asthmatic attack, significantly lowered the specific airway resistance in these mice. Specification at page 24, line 5 to page 25, line 17; and Figs. 5A and 5B. At page 27, line 11 to page 28, line 18 of the specification, the inventor further reported that aerosol administration of an anti-C5 antibody to mice during an asthmatic attack had a significant therapeutic effect on airway responsiveness as measured by the antibody's effect on bronchial dilation. The specification also describes that the anti-C5 antibody significantly reduced the concentration of invading white blood cells (predominantly eosinophils, as one characteristic of asthma) in the lungs of treated mice. *See* specification at, e.g., page 25, line 20 to page 27, line 10; and Fig. 8. These results indicate that an anti-C5 antibody is useful for treating subjects with established airway disease (e.g., asthma), as is presently claimed.

In contrast to Applicant's disclosure, Krause describes a series of candidate small molecule C5a receptor antagonists and suggests, but does not experimentally demonstrate, that they may be useful for treating inflammatory diseases. As discussed above, the reference twice recites eculizumab and pexelizumab (at paragraphs [0207] and [0277]), in each instance listed, along with a laundry list of other well-known putative anti-arthritic agents[6], for use in treating rheumatoid

[6] Notably, at the effective date of Krause, Alexion Pharmaceuticals, Inc. was engaged in a well-known phase II clinical trial evaluating an anti-C5 antibody in rheumatoid arthritis. *See, e.g.*, PR Newswire article dated 4 August 1999 and Abstract of Kaplan (2002) *Curr Opin Investig Drugs* 3(7):1017-1023 (stating that - "Eculizumab … is under development by Alexion as a potential treatment for … rheumatoid arthritis (RA) … In January 2002, a phase IIb trial was initiated for RA"), submitted herewith as Exhibit D.

arthritis. The reference does not expressly or inherently disclose methods for using anti-C5 antibodies as instantly claimed (*supra*).

The Office Action, however, advances the following syllogism: Krause discloses that inhibiting C5a receptor signaling (using candidate small molecule compounds) may be useful for treating asthma; anti-C5 antibodies inhibit the production of C5a; therefore, a skilled artisan reading Krause allegedly would have believed that anti-C5 antibodies are useful for treating asthma. Yet "[a] person of ordinary skill is…not an automaton." *KSR International Co.*, 550 U.S. at 421. The artisan would have considered ***all teachings in the analogous prior art*** and what the combined teachings suggested. The Examiner, by proxy, must do the same. M.P.E.P. § 2143.01 (II). According to the CAFC,

> [w]here the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another.

In re Young, 927 F.2d 588 (Fed. Cir. 1991). Such is the case at bar.

At the effective filing date of the instant application, the art was, at best, conflicted about the role of complement component C5 in asthma. As evidence of the state of the art at the priority date of the application, Applicant again provides Karp et al. (2000) *Nature Immunology* 1(3):221[7] [hereinafter Karp], a reference published two years prior to the effective filing date of Krause. Karp's authors found that lower expression of C5 protein is associated with more severe OVA-induced inflammation in mouse lung (see Figure 1). These actual experimental results, of course, are in stark contrast to what a skilled artisan would have expected under the Examiner's interpretation of the Krause reference.

In addition, Karp discloses that inhibition of C5a receptor, as is at issue in Krause, results in a marked reduction in IL-12 production by monocytes *in vitro* (see Figure 3). IL-12 is a cytokine that is able to prevent or reverse experimental allergic asthma (see Abstract of Karp). This disclosure would very likely lead a skilled artisan to believe that inhibition of C5 would, if anything, exacerbate asthma, rather than treat it. Thus, Applicant submits that Karp ***teaches away*** from the

[7] Karp was provided by Applicant as Exhibit A in the 8 December 2008 Amendment and Response to Office Action.

notion that inhibition of C5a or C5 would reduce the severity of OVA-induced inflammation in mouse lung. Accordingly, the skilled artisan reading Karp would have believed that C5 was protective against asthma and that inhibition of C5 or C5a receptor would not be beneficial for treating asthma.

Such a belief is consistent with other reports published proximal to the filing date of the instant application, and further teaching away from any benefit of using C5 inhibitors to treat respiratory disorders such as asthma. For example, Humbles et al. (2000) *Nature* 406:998-1001 [hereinafter Humbles][8], a reference published two years before the effective filing date of Krause, demonstrates that mice deficient in C3a receptor alone were protected against methacholine-induced airway hyperresponsiveness in a mouse model of asthma. *See* Humbles at, e.g., page 999, Figure 3.

C3a is a cleavage product of complement component C3, which is upstream of C5. As expressly acknowledged by the Office Action, "C5 blockade preserves the critical … immunoregulatory functions of upstream components" such as C3. Office Action at page 9. Given the art-recognized critical role for C3a/C3a receptor in asthma, and that the pathophysiological action of C3a is not inhibited by C5 antagonists, one of skill in the art at the effective date of this application would very likely have believed that inhibition of C5a alone, or C5, would not prevent C3-driven airway hyperresponsiveness in asthma.

Krause's disclosure does not surmount the contrary teachings in the art. For example, Krause provides absolutely no experimental evidence that its C5a receptor antagonists are effective at treating asthma in an animal model, let alone in humans. On its face, Krause does not even experimentally demonstrate that its compounds are capable of inhibiting C5a receptor signaling. To wit: although Krause describes through a series of prophetic examples how one *could* test its small molecule compounds for *in vitro* activity (e.g., inhibition of C5a receptor-mediated signal transduction), there is no evidence that any of its putative C5a receptor antagonists *were actually tested* and confirmed to have such activity. The skilled artisan steeped in the art would have recognized Krause as espousing little more than hypothetical, conjectural, and/or hoped-for results.

[8] Humbles was provided by Applicant as Exhibit D in the 8 December 2008 Amendment and Response to Office Action.

Notably, Neurogen, the assignee of the Krause application, supported a randomized clinical trial involving 142 patients with mild-to-moderate asthma, who were treated with a small molecule C5a antagonist – NGD-2000-1 – in a manner consistent with the Krause disclosure. The trial failed in 2004 with results showing no therapeutic benefit. *See*, e.g., Press Release dated 13 January 2004 (a copy of which is submitted herewith as Exhibit E). The Krause disclosure simply would not have been sufficient in the mid of a skilled artisan to overcome the strong contrary experimental evidence present in the art. The artisan's reticence was vindicated by Neurogen's failed clinical trial. Thus, absent the express teachings of the instant application, the skilled artisan reading Krause would not have had the requisite reason to practice the instantly claimed methods.

The secondary references cited by the Office do not cure the large deficiencies of Krause. For example, Fung (a), as acknowledged by the Office Action, relates to anti-factor D antibodies. The Office asserts that Fung (a), particularly at column 9, teaches the role of C5a, and inhibition thereof, in the context of severe asthma. Applicant respectfully disagrees.

In contrast to the Office Action's characterization, of Fung (a) at column 9 discloses textbook knowledge that anti-factor D antibodies, by virtue of acting upon the C3 convertase step of the complement cascade, inhibit downstream complement activation including the generation of C5a and C5b-9. Column 9, lines 39 to 41. Notably, inhibition of factor D using anti-factor D antibodies inhibits the production of C3a (Fung (a) at column 9, line 40), which, as noted above, was described by Humbles to play a critical role in airway hyperreactivity. There is simply no disclosure or suggestion in Fung (a) that C5a receptor antagonists, let alone anti-C5 antibodies, are, or would be, useful for treating asthma as is instantly claimed.

Fung (b) exhibits similar deficiencies. The reference relates to anti-C2a antibodies and their use in treating complement-associated diseases. At page 10 the Office Action urges that Fung (b) teaches that anti-C2a antibodies, by virtue of acting upon the C3 convertase step of the complement cascade, inhibit downstream complement activation including the generation of C5a and C5b-9. Yet there is no disclosure or suggestion in this reference that inhibition of C5 is therapeutically useful as claimed.

As with Fung (a) and Fung (b), neither Evans nor Lobb remedies the deficiencies of the primary reference. Evans discloses and claims a genus of new anti-C5 antibodies. The reference, as cited by the Examiner, states that the antibodies can be used "for treatment of other inflammatory conditions involving pathogenic activation of complement system." Lobb does not even relate to inhibition of the complement cascade, but is offered by the Examiner as evidence of combination therapies and that an antibody can be delivered to the lungs of a subject. Office Action at page 11. The references do not, however, disclose or suggest the instantly claimed methods or otherwise suggest an alternative view to that advanced by Humbles and Karp.

In conclusion, it is clear that absent the teachings of the instant specification, there would have been no apparent reason for a skilled artisan to modify the teachings of Krause, in view of the secondary references, and arrive at the claimed methods. None of the cited references, including Krause, sets forth any data evidencing use of any C5 inhibitor, let alone an anti-C5 antibody, in the instantly claimed methods. The cited references also fail to surmount the teachings of, e.g., Humbles and Karp, which argued against therapeutic C5 inhibition in asthma. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103.

Double Patenting

At page 12 of the Office Action, claims 1 to 11, 15 to 18, 20, 21, 45 to 51, 59, and 60 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 31 to 35 and 48 of copending patent application no. 11/127,438.

Pursuant to MPEP § 804, as the instant application is the earlier filed application and this provisional rejection will be the only remaining rejection after Applicant's arguments are sustained, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection and allow the case to issue without a terminal disclaimer.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant submits that the pending claims are in condition for allowance. Early and favorable consideration is respectfully solicited.

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicant believes no fees are due other than specifically itemized on the accompanying fee transmittal. However, should an extension of time be required, Applicant hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to Deposit Account No. 18-1945, under Order No. ALXN-P01-102 from which the undersigned is authorized to draw.

Dated: July 18, 2011

Respectfully submitted,

By /Jason Cathelyn/
Jason S. Cathelyn, Ph.D.
Registration No.: 68,195
ROPES & GRAY LLP
Prudential Tower
800 Boylston Street
Boston, Massachusetts 02199
(617) 951-7000
(617) 235-9492 (Fax)
Attorneys/Agents For Applicant